PATENT COOPERAT IN TREATY

	From the INTERNATIONAL BUREAU
PCT	To:
NOTIFICATION OF ELECTION (PCT Rule 61.2)	Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE
Date of mailing (day/month/year) 14 November 2000 (14.11.00)	in its capacity as elected Office
International application No.	Applicant's or agent's file reference
PCT/EP00/02467	ML/B45182
International filing date (day/month/year)	Priority date (day/month/year)
17 March 2000 (17.03.00)	19 March 1999 (19.03.99)
Applicant	
CAPIAU, Carine et al	
1. The designated Office is hereby notified of its election made with the International Preliminar 13 October 20 in a notice effecting later election filed with the International Preliminar 13 October 20 The election X was was not made before the expiration of 19 months from the priority Rule 32.2(b).	y Examining Authority on: 00 (13.10.00) national Bureau on:
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Mafla

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 GB

 9916677.9
 15 July 1999 (15.07.1999)
 GB

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- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- (88) Date of publication of the international search report: 1 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

0/56359 A3

(54) Title: VACCINE AGAINST STREPTOCOCCUS PNEUMONIAE

(57) Abstract: The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to vaccines comprising a pneumococcal polysaccharide antigen, typically a pneumococcal polysaccharide conjugate antigen, formulated with a protein antigen form *Streptococcus pneumoniae*, and optionally a Th1-inducing adjuvant.

nal Application No PCT/EP 00/02467

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K39/09 A61K39/385 A61P31/04 A61K39/39

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

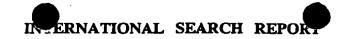
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 06951 A (PATON JAMES CLELAND; HANSMAN DAVID JOHN (AU); MITCHELL TIMOTHY JOH) 28 June 1990 (1990-06-28) cited in the application page 3, line 35 -page 4, line 23 page 10, line 1 - line 3	1-9, 13-18
Υ	claims 1-14	10-12
X	LEE C J ET AL: "Immunologic epitope, gene, and immunity involved in pneumococcal glycoconjugate." CRITICAL REVIEWS IN MICROBIOLOGY, vol. 23, no. 2, 1997, pages 121-141, XP000946772	1-7, 13-18
Y	the whole document, especially page 132 column 2 line 27 - page 135 column 2 line 18	8-12
	 -/	

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents : A* document defining the general state of the art which is not considered to be of particular relevance.	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	30/10/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2	Authorized officer
NL – 2280 HV Rîjswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Stein, A



Interr nal Application No PCT/EP 00/02467

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	· · · · · · · · · · · · · · · · · · ·
ategory "	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
X	BRILES DAVID E ET AL: "Pneumococcal diversity: Considerations for new vaccine strategies with emphasis on pneumococcal surface protein A (PspA)." CLINICAL MICROBIOLOGY REVIEWS, vol. 11, no. 4, October 1998 (1998-10), pages 645-657, XP000946754 ISSN: 0893-8512	1-7, 13-18
Υ	the whole document especially page 646 column 1 line 35 - page 646 column 2 line 9; page 653 column 1 line 27-46	8-12
Y	WO 96 33739 A (SMITHKLINE BEECHAM BIOLOG;GARCON NATHALIE MARIE JOSEPHE (BE); FRI) 31 October 1996 (1996-10-31) cited in the application page 1, line 1 -page 3, line 21 claims 1,5,8-10,12	8-12
X	ALEXANDER JANET E ET AL: "Immunization of Mice with Pneumolysin Toxoid Confers a Significant Degree of Protection against At Least Nine Serotypes of Streptococcus pneumoniae." INFECTION AND IMMUNITY, vol. 62, no. 12, 1994, pages 5683-5688, XP002149967 ISSN: 0019-9567 page 5683, column 1, line 26 -column 2, line 8 page 5687, column 1, line 51 - line 58	1-5, 13-18
Α	MICHON F ET AL: "Multivalent pneumococal capsular polysaccharide conjugate vaccines employing genetically detoxified pneumolysin as a carrier protein" VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 18, 1998, pages 1732-1741, XP002089380 ISSN: 0264-410X the whole document	1-5,7-9, 13-18
Α	DE VELASCO E ALONSO ET AL: "Synthetic peptides representing T-cell epitopes act as carriers in pneumococcal polysaccharide conjugate vaccines." INFECTION AND IMMUNITY, vol. 63, no. 3, 1995, pages 961-968, XP002149966 ISSN: 0019-9567 the whole document	1-5, 8-11, 13-18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)



Interr nal Application No PCT/EP 00/02467

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C.(Continu Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
A	WO 95 17209 A (SMITHKLINE BEECHAM BIOLOG; MOMIN PATRICIA MARIE (BE); GARCON NATHA) 29 June 1995 (1995-06-29) cited in the application page 4, line 26 -page 5, line 16 claims 1-5,8-10,12,13	10-12



Information on patent family members

Interr nal Application No PCT/EP 00/02467

Patent document cited in search report	Publication date		atent family nember(s)	Publication date
WO 9006951 A	28-06-1990	AU AU	626961 B 4756490 A	13-08-1992 10-07-1990
		BG	51358 A	15-04-1993
		CĀ	2005704 A	16-06-1990
		DK	115591 A	14-08-1991
		EP	0449856 A	09-10-1991
		FI	103122 B	30-04-1999
		HU	58804 A	30-03-1992
		JP	4503948 T	16-07-1992
		MC	2178 A	22-05-1992
		NO	304317 B	30-11-1998
		RU	2121481 C	10-11-1998
WO 9633739 A	31-10-1996	AP	771 A	07-10-1999
		AT	186842 T	15-12-1999
		AU	693022 B	18-06-1998
		AU	5334596 A	18-11-1996
		AU	699213 B	26 - 11-1998
		AU BG	6987398 A 101995 A	23-07-1998 30-11-1998
		BR	9608199 A	30-11-1998 18-05-1999
		CA	2217178 A	31-10-1996
		CN	1182370 A	20-05-1998
		CZ	9703379 A	18-03-1998
		DE	69605296 D	30-12-1999
		DE	69605296 T	18-05-2000
		ΕP	0822831 A	11-02-1998
		EP	0884056 A	16-12-1998
		EP	0955059 A	10-11-1999
		ES	2140076 T	16-02-2000
		GR	3031912 T	29-02-2000
		HU	9801560 A	28-10-1998
		JP	11504020 T	06-04-1999
		NO NZ	974859 A	21-10-1997
		NZ Pl	305365 A 322968 A	28-05-1999 02-03-1998
		SI	822831 T	29-02-2000
		SK	144297 A	06-05-1998
		ZA	9602612 A	29-08-1996
			*	
WO 9517209 A	29-06-1995	AT	177322 T	15-03-1999
		AU	1316495 A	10-07-1995
		AU AU	687494 B 1316695 A	26-02-1998 10-07-1995
		AU	705521 B	27-05-1999
		AU	6803198 A	09-07-1998
		AU	705519 B	27-05-1999
		AU	6803298 A	09-07-1998
		CA	2179779 A	29-06-1995
		CN	1138298 A	18-12-1996
		DE	69417063 D	15-04-1999
		ÐΕ	69417063 T	28-10-1999
		DK	735898 T	23-08-1999
		MO	9517210 A	29-06-1995
		ΕP	0735898 A	09-10-1996
				07 10 1000
		EP	0868918 A	07-10-1998
		EP ES GR	0868918 A 2129801 T 3029750 T	07-10-1998 16-06-1999 30-06-1999



Information on patent family members

Interr nal Application No PCT/EP 00/02467

Patent document cited in search report	Publication date		ratent family member(s)	Publication date
WO 9517209 A		JP NZ SG SI ZA	9506887 T 277802 A 49257 A 735898 T 9410176 A	08-07-1997 27-04-1998 18-05-1998 30-06-1999 17-11-1995

Form PCT/ISA/210 (patent family annex) (July 1992)

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PATENT COOPERSION TREATY REC'D 16 MAR 2001

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REC'D 16 MAR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's	or age	nt's file reference				ation of Transmittal of International
ML/B451	82		FOR FURTHER ACTIO	NC	Preliminary	Examination Report (Form PCT/IPEA/416)
Internationa	ıl appli	cation No.	International filing date (day/	nonth/	year)	Priority date (day/month/year)
PCT/EPC	0/02	467	17/03/2000			19/03/1999
A61K39/		nt Classification (IPC) or	national classification and IPC			
• •	INE	BEECHAM BIOLO	GICALS S.A.		****	
1. This i	nterna trans	ational preliminary examitted to the application	amination report has been prent according to Article 36.	pared	by this Inte	mational Preliminary Examining Authority
2. This I	REPO	RT consists of a total	of 7 sheets, including this co-	ver sh	eet.	
b (s	een a see R	mended and are the ule 70.16 and Section	basis for this report and/or she n 607 of the Administrative Inst	ets co	ntaining re	n, claims and/or drawings which have ctifications made before this Authority ne PCT).
These	anne	exes consist of a total	of 3 sheets.			
			•			
3. This r		,	relating to the following items:			-
	⊠ □	Basis of the report		•		
·	□ IXI	Priority	of opinion with regard to novelt	y inve	entive sten	and industrial applicability
III IV	⊠ □			у, п	HILLY STOP	and modelial applicability
v	⊠	Reasoned statemen		rd to n	ovelty, inve	entive step or industrial applicability;
VI		Certain documents				
VII	\boxtimes	Certain defects in th	e international application			
VIII		Certain observations	s on the international application	on		
Date of sub	missio	on of the demand	Da	ite of c	ompletion of	this report
13/10/20	00		13	.03.20	01	·
		address of the internati	onal Au	 ithorize	ed officer	AND THE PARTY OF T
preliminary	Euro D-80	ining authority: opean Patent Office 0298 Munich +49 89 2399 - 0 Tx: 523		niele,	U	
		+49 89 2399 - 4465	*	lephon	e No. +49 8	9 2399 8643

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02467

 Basis of the report 	ا ا	Basi	s o	f the	rep	or	t
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۱.	res _i the	oonse to an invitatio	rawn on the basis of (subs on under Article 14 are refe o not contain amendments	erred to in this repo	rt as "originally fil		
	1-7	2	as originally filed				
	Cla	ims, No.:					
	1-1	5	as received on	05/03/2001	with letter of	02/03/2001	
	Dra	wings, sheets:					
	1/1		as originally filed				
2.			juage , all the elements ma international application wa				
	The	se elements were a	available or furnished to th	is Authority in the fo	ollowing language	: , which is:	
		the language of a	translation furnished for th	e purposes of the i	nternational searc	ch (under Rule 23.1(b)).	
		the language of pu	ublication of the internation	al application (und	er Rule 48.3(b)).		
		the language of a 55.2 and/or 55.3).	translation furnished for th	e purposes of inter	national prelimina	ry examination (under Ru	ile
3.			eleotide and/or amino aci y examination was carried	=			
		contained in the in	ternational application in v	vritten form.			
		filed together with	the international application	on in computer read	lable form.		
		furnished subsequ	ently to this Authority in w	ritten form.			
		furnished subsequ	ently to this Authority in co	omputer readable fo	orm.		
			t the subsequently furnish pplication as filed has bee	•	e listing does not	go beyond the disclosure	in
		The statement tha listing has been fu	t the information recorded rnished.	in computer readal	ble form is identic	al to the written sequence	ł
١.	The	amendments have	resulted in the cancellation	on of:			
		the description,	pages:				
		the claims,	Nos.:				

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02467

		•
		the drawings, sheets:
5.		This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
		(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6.	Add	itional observations, if necessary:
111.	Nor	establishment of opinion with regard to novelty, inventive step and industrial applicability
1.		questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- ious), or to be industrially applicable have not been examined in respect of:
		the entire international application.
	×	claims Nos. 12,15.
be	caus	e:
	×	the said international application, or the said claims Nos. 12,15 relate to the following subject matter which does not require an international preliminary examination (<i>specify</i>): see separate sheet
		the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
		the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
		no international search report has been established for the said claims Nos
2.	and	eaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide for amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative ructions:
		the written form has not been furnished or does not comply with the standard.
		the computer readable form has not been furnished or does not comply with the standard.
V.		soned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; tions and explanations supporting such statement
1.	Stat	ement
	Nov	elty (N) Yes: Claims 1-15

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/EP00/02467

No:

Claims

Inventive step (IS)

Yes:

Claims 1-15

No:

Claims

Industrial applicability (IA)

Yes:

Claims 1-11,13,14

No:

Claims 12?,15?(see section III)

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

Section III

Claims 12 and 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section V

Reference is made to the following documents: 1)

D1: WO 90 06951 A

D2: CRITICAL REVIEWS IN MICROBIOLOGY, vol. 23, no. 2, 1997, pages 121-

141 .

D3: CLINICAL MICROBIOLOGY REVIEWS, vol. 11, no. 4, October 1998, pages

645-657

D4: INFECTION AND IMMUNITY, vol. 62, no. 12, 1994, pages 5683-5688

D5: VACCINE, GB, BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 16, no. 18,

1998, pages 1732-1741

D6: WO 96 33739 A

The subject-matter of claim 1 would appear to be novel and inventive in view of 2) the known state of the art (Art. 33(2), (3) PCT).

D1 (see esp. page 2, line 16 - page 4, line 23; page 10, lines 1 - 3; claims 9 - 14, claim 23) merely discloses vaccines comprising at least one Streptococcus

pneumoniae polysaccharide antigen and the S. pneumoniae protein antigen pneumolysin in a mutated form, and the preparation thereof. The polysaccharide may be derived from a poly-, esp. 23valent vaccine. Adjuvants such as alumina gel may be added. The antigen / polysaccharide complex is either conjugated or non conjugated. Carrier proteins such as tetanus toxoid are mentioned. The vaccine aims at protecting young children from pneumococcal infection.

D2 (see esp. page 132, col. 2, line 27 - page 135, col. 2, line 18) merely pertains to pneumococcal glycoconjugate vaccines. To this end, inactivated pneumolysin or pneumococcal surface protein A is conjugated to one or more pneumococcal polysaccharides. Carrier proteins such as tetanus toxoid are mentioned. The vaccine aims at protecting infants and the elderly (see page 121, r. col.).

D3 (page 646, chapter headed "Polysaccharide-Protein Conjugate [...]"; page 653, chapter headed "Potential use of PspA [...]") merely suggests in particular the use of Pneumococcal surface protein A as a carrier for pneumococcal polysaccharides in vaccines for young children and the elderly.

D4 overcomes the poor immunogenicity of (multivalent) S. pneumoniae polysaccharides in vaccines by including pneumococcal proteins, in particular pneumolysin toxoids, either as protein carrier and/or as protective immunogen in their own right (see esp. page 5683, r.col., lines 4 - 8; p. 5687, "Conclusion").

Lastly, D5 is merely concerned with detoxified pneumolysin as a carrier protein for pneumococcal capsular polysaccharides.

None of the said documents however contemplates the use of an adjuvant which is a preferential inducer of a Th1 response.

Although D6 (see pages 1, 2; claims 1, 5, 8 - 10, 12) discusses such Th1 adjuvants, there is no mention of how it could aid the coordination of humoral and cell-mediated immune responses against pneumococci when present in a composition further comprising a pneumococcal polysaccharide and protein, this being the unexpected effect resulting from the feature distinguishing the subjectmatter of claim 1 from D1 - D5. D6 rather teaches that necrosis at the injection site of vaccination can be avoided by use of formulations containing a combination of such adjuvant and a sterol.

The afore mentioned advantages of the present invention are apparent from the description, page 16, line 27 - page 17, line 6; page 60, lines 8 - 12; and Examples 4B and 4C.

3) Independent claims 10 - 15 rely on the same novel and inventive concept as claim 1 and therefore, together with dependent claims 2 - 9, also meet the requirements of Arts. 33(2) and (3) PCT.

Section VII

- 1) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 D5 is not mentioned in the description, nor are these documents identified therein.
- 2) The description has not been adapted to the wording of the amended claims (Guidelines C-III, 4.3)

Additional note: The applicant submitted written evidence (PubMed entries with PMIDs 11115692, 10217586, 9726341 and 9674889) for a general acceptance of the said term "CRM197" in the technical field concerned.



Claims:

1. An immunogenic composition comprising at least one Streptococcus pneumoniae polysaccharide antigen and at least one Streptococcus pneumoniae protein antigen or immunologically functional equivalent thereof.

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- 2. The immunogenic composition of claim 1, wherein the protein antigen is an outer surface protein or a secreted protein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.
- 10 3. The immunogenic composition of claims 1 or 2, wherein the protein antigen is a toxin, adhesin or lipoprotein of *Streptococcus pneumoniae* or immunologically functional equivalents thereof.
- 4. The immunogenic composition of claims 1-3, wherein the protein antigen or immunologically functional equivalent thereof is selected from the group: pneumolysin, PspA or transmembrane deletion variants thereof, PspC or transmembrane deletion variants thereof, PsaA or transmembrane deletion variants thereof, glyceraldehyde-3-phosphate dehydrogenase, and CbpA or transmembrane deletion variants thereof.

- 5. The immunogenic composition of claims 1-4, wherein the polysaccharide antigen is presented in the form of a polysaccharide-protein carrier conjugate.
- The immunogenic composition of claim 5, wherein the carrier protein is
 selected from the group consisting of: Diphtheria toxoid, Tetanus toxoid, CRM197,
 Keyhole Limpet Haemocyanin (KLH), protein derivative of Tuberculin (PPD), and
 protein D from H. influenzae.
- An immunogenic composition as claimed in any of claims 1 to 6 wherein the
 vaccine comprises at least four pneumococcal polysaccharide antigens from different serotypes.



- 8. An immunogenic composition as claimed herein additionally comprising an adjuvant.
- 9. An immunogenic composition as claimed in claim 8, wherein the adjuvant
 5 comprises an aluminium salt.
 - 10. An immunogenic composition as claimed in claim 8, wherein the adjuvant is a preferential inducer of a TH1 response.
- 10 11. An immunogenic composition as claimed in claim 10, wherein the adjuvant comprises at least one of the following: 3D-MPL, a saponin immunostimulant, or an immunostimulatory CpG oligonucleotide.
- 12. An immunogenic composition as claimed in claim 11, wherein the adjuvant comprises a carrier selected from the group comprising: an oil in water emulsion, liposomes, and an aluminium salt.
 - 13. An immunogenic composition composition as claimed herein for use as a medicament.
- 14. A vaccine comprising the immunogenic composition of claims 1-12.
- 15. A method of preventing or ameliorating Streptoccocus pneumoniae infection in a patient over 55 years, comprising administering an effective amount of a vaccine
 25 comprising a Streptococcus pneumoniae polysaccharide and at least one Streptococcus pneumoniae protein, and optionally a TH1 inducing adjuvant.
- 16. Use of a pneumococcal polysaccharide antigen in combination with a Streptoccocus pneumoniae protein antigen, and optionally a TH1 inducing adjuvant,
 30 in the manufacture of a medicament for the prevention of pneumonia in patients over 55 years.



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17. A method of making an immunogenic composition as claimed herein, comprising the steps of:

selecting one or more pneumococcal polysaccharide antigen(s); selecting one or more pneumococcal protein antigen(s); and mixing said polysaccharide and protein antigens with a suitable excipient.

18. A method of preventing or ameliorating Otitis media in Infants, comprising administering a safe and effective amount of a vaccine comprising a *Streptococcus pneumoniae* polysaccharide antigen and a *Streptococcus pneumoniae* protein antigen optionally with a TH1 adjuvant, to said Infant.



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(57) Abstract

The present invention relates to the field of bacterial polysaccharide antigen vaccines. In particular, the present invention relates to vaccines comprising a pneumococcal polysaccharide antigen, typically a pneumococcal polysaccharide conjugate antigen, formulated with a protein antigen form *Streptococcus pneumoniae*, and optionally a Th1-inducing adjuvant.

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